Beth Israel Lahey Health Direct Oral Anticoagulant (DOAC) Selection Guide

The following information is designed to guide and inform prescribers on the selection of DOACs for ambulatory patients at the point of prescribing.

Step 1: Assess Patient-Specific Anticoagulation Plan

- Review anticoagulation indication and planned duration of therapy. Refer to "VTE Duration of Therapy Recommendations" section (link)
- Incorporate patient preferences, values, and acceptance of anticoagulation during shared decision making discussion

Step 2: Assess Clinical Appropriateness for DOAC Therapy

Do Not Use DOACs in the following patient populations:	**Use caution in the following patient populations:**
• Mechanical Heart Valves or Valvular heart disease (i.e. moderate to severe mitral stenosis or rheumatic valve disease) • Acute renal failure or fluctuating/unstable renal function • Moderate or severe liver disease (Child Pugh Class B or C) • Triple Positive Antiphospholipid Antibody Syndrome • Pregnant or breastfeeding **Consider alternative anticoagulation with warfarin or enoxaparin and/or specialist consultation**	• Extremes of body weight (i.e. </= 50 kg or >/= 150 kg) • Poor renal function (CrCl < 30 mL/min) • GI/GU Cancers • History of bariatric surgery

Step 3: Assess Medication Adherence

- History of missing oral medication doses?
  - DOACs have short half-lives. One or two missed doses have the potential to result in subtherapeutic anticoagulation.
  - If improved adherence is not obtainable, warfarin may be a more optimal anticoagulant given its longer half-life and clinic oversight.
    - Lab draw adherence will also need to be assessed and discussed.

Step 4: Assess for Significant Medication Interactions

- **DO NOT USE** with combined strong CYP3A4 and/or P-glycoprotein inhibitors and/or inducers. Refer to "Drug Interactions" section (link) for specific assessment information to answer the question "does a significant interaction exist?"
  - **Consider warfarin given the ability to monitor INR and adjust warfarin dose accordingly.**
- For patients on antiplatelet medications (e.g. aspirin, clopidogrel, prasugrel, ticagrelor), please review indication/duration/continued clinical appropriateness of these meds before initiating anticoagulation and de-prescribe if clinically appropriate.

Step 5 Assess Potential Inability to Afford DOAC

- Determine the patient's insurance coverage, eligibility for patient assistance programs, and total out of pocket costs.
  - Warfarin is an option for patients with high out of pocket costs.
  - Patients with plans that cover DOACs may still have high out of pocket costs (i.e. copays, deductibles and the annual "donut hole").

Refer to the DOAC Cost and Coverage chart for more information to guide shared decision making discussions around "is the patient unable to afford DOAC therapy?"

Step 6 Determine DOAC of Choice

- Refer to the details in the BILH DOAC Prescribing Guide in the following pages to select the most appropriate DOAC and dose.

Approved:
BILH Ambulatory P&T 10/2021
BILH System P&T 12/2021

Important Note: This guide does not replace clinical judgment.

Always consider consultation with a specialist if clinical circumstances are not addressed within this guide or if clarification is needed for an individual patient scenario.

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12/2021

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Indication and Dosing Comparison Chart

	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Edoxaban (Savaysa)
Mechanism	Direct Xa Inhibitor	Direct Xa inhibitor	Direct Thrombin Inhibitor	Direct Xa Inhibitor
FDA-Approved Indication and Dosing →***See individual drug information for drug interaction adjustments***				
Non-Valvular Atrial Fibrillation	**STANDARD DOSE:** 5 mg BID **DOSE ADJUSTMENT:** 2.5 mg BID if at least two of the following criteria met: • Age ≥ 80 years • Weight ≤ 60 kg • Serum creatinine ≥ 1.5 mg/dL **USE WITH CAUTION:** CrCl less than 25 mL/min Consider risk-benefit. Limited data supports potential safe use in ESRD with/without dialysis.	**STANDARD DOSE:** 20 mg daily with largest meal of the day **DOSE ADJUSTMENT:** • CrCl 15-50 mL/min: 15 mg daily with food **DO NOT USE:** CrCl less than 15 mL/min	**STANDARD DOSE:** 150 mg BID **DOSE ADJUSTMENT:** CrCl 15-30 mL/min: 75 mg BID **DO NOT USE:** CrCl less than 15 mL/min	**STANDARD DOSE:** 60 mg daily **DOSE ADJUSTMENT:** CrCl 15-50 mL/min: 30 mg daily **DO NOT USE:** • CrCl less than 15 mL/min • CrCl greater than 95 mL/min
Acute VTE Treatment	**STANDARD DOSE:** 10 mg BID x 7 days, **then decrease to** 5 mg BID **Note: Starter pack recommended for first month of treatment only** **DO NOT DOSE ADJUST** **USE WITH CAUTION:** CrCl less than 25 mL/min Consider risk-benefit. Limited data supports potential safe use in ESRD with/without dialysis.	**STANDARD DOSE:** 15 mg BID with food for 21 days **then decrease to** 20 mg daily with largest meal of the day to continue **Note: Starter pack recommended for first month of treatment only** **DO NOT DOSE ADJUST** **DO NOT USE:** CrCl less than 30 mL/min	**STANDARD DOSE:** After 5-10 days of initial heparin or LHWH therapy, start 150 mg BID **DO NOT DOSE ADJUST** **DO NOT USE:** CrCl less than 30 mL/min	**STANDARD DOSE:** After 5-10 days of initial heparin or LMWH therapy, start 60 mg daily **DOSE ADJUSTMENT:** CrCl 15-50 mL/min **OR** weight ≤ 60 kg: 30 mg daily **DO NOT USE:** CrCl less than 15 mL/min

	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Edoxaban (Savaysa)
Reduction in the risk of recurrence of VTE (following at least 6 months of initial treatment for VTE) **Note**: **Use of reduced dose apixaban or rivaroxaban is not recommended in patients with**: • Antiphospholipid antibody syndrome • Atrial fibrillation • Active cancer **Consider specialty consult if needed**	**STANDARD DOSE:** 5mg BID or **REDUCED DOSE:** 2.5 mg BID Consider patient specific risk factors for thrombosis and bleeding when choosing the appropriate dose for extended therapy **USE WITH CAUTION:** CrCl less than 25 mL/min or SCr greater than 2.5 mg/dL	**STANDARD DOSE:** 20 mg daily with largest meal of the day or **REDUCED DOSE:** 10 mg daily (with/without food) Consider patient specific risk factors for thrombosis and bleeding when choosing the appropriate dose for extended therapy **DO NOT USE:** CrCl less than 15 mL/min	**STANDARD DOSE:** 150 mg BID **DO NOT USE:** CrCl less than 30 mL/min	**STANDARD DOSE:** 60 mg daily **DOSE ADJUSTMENT:** CrCl 15-50 mL/min **OR** weight ≤ 60 kg: 30 mg daily **DO NOT USE:** CrCl less than 15 mL/min
VTE prophylaxis – Hip	**STANDARD DOSE:** 2.5 mg BID x 35 days **USE WITH CAUTION:** CrCl less than 30 mL/min	**STANDARD DOSE:** 10 mg daily x 35 days **DO NOT USE:** CrCl less than 30 mL/min	**STANDARD DOSE:** 110 mg on day 1, then 220 mg daily for 28-35 days **DO NOT USE:** CrCl less than 30 mL/min	
VTE prophylaxis – Knee	**STANDARD DOSE:** 2.5 mg BID x 12 days **DO NOT USE:** CrCl less than 30 mL/min	**STANDARD DOSE:** 10 mg daily x 12 days		
VTE prophylaxis in acutely ill medical patients at risk for thromboembolic complications, not at high risk of bleeding		**STANDARD DOSE:** 10 mg daily, in hospital and after hospital discharge for a total of 31 to 39 days **DO NOT USE:** CrCl less than 30 mL/min		
Reduction of risk of major cardiovascular events in chronic CAD or PAD		**STANDARD DOSE:** 2.5 mg BID with aspirin 81 mg daily **DO NOT USE:** CrCl less than 30 mL/min		

	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Edoxaban (Savaysa)
Dosage Forms and Administration Notes: Patients with Swallowing Difficulties	• Can be crushed and given with applesauce • Can be administered down NG or gastric feeding tube. • Not scored. Ideally tablets should not be split to ensure accurate dosing	• Can be crushed and given with applesauce • Can be administered down NG or gastric feeding tube. May then be followed with enteral feeding • Not scored. Ideally tablets should not be split to ensure accurate dosing • Doses of 10 mg or less do not need to be taken with food	• Must be swallowed whole	• Can be crushed and given with applesauce • Can be administered down NG or gastric feeding tube. • Not scored. Ideally tablets should not be split to ensure accurate dosing
Suggested Monitoring	• **Annually:** Renal function if CrCl > 60 mL/min, liver function, CBC, and medication adherence before initiation and at least yearly • **Every 6 months:** Renal function if CrCl 31-60 mL/min • **Every 3 months:** Renal function if CrCl </= 30 mL/min, on rivaroxaban with CrCl 15-60 mL/min, or on dabigatran and > 75 years or fragile ***Use Cockcroft–Gault with actual body weight to calculate creatinine clearance (CrCl)*** • ***Calculator available in UptoDate or Global RPh CrCl Calculator***			

VTE Duration of Therapy Recommendations

For the majority of patients undergoing initial VTE treatment:

- Provoked DVT of leg or PE (by surgery or transient/reversible risk factor): 3 months is the recommended length of treatment.
- Unprovoked DVT of leg or PE: treat for 3 months and then re-evaluate the risk-benefit analysis for continued anticoagulation.
- Recurrent VTE: consider indefinite anticoagulation based on risk-benefit analysis.
- Active cancer: indefinite anticoagulation is recommended.

Long-term secondary prevention after 6-12 months of anticoagulation (can be considered in patients who have completed their initial period of treatment but have continued need for anticoagulation):

- Patients with continued need for anticoagulation due to risk of VTE recurrence, options include:
  - reduced dose rivaroxaban (10 mg daily),
  - reduced dose apixaban (2.5 mg BID),

  Use of reduced dose apixaban or rivaroxaban is not recommended in patients with antiphospolipid antibody syndrome, atrial fibrillation or active cancer. Consider specialty consult if needed.
  - continued full dose dabigatran (150 mg BID), or
  - continued warfarin or LMWH.
- Aspirin should not be first choice for long-term secondary prevention of VTE

Drug Interactions*
Pharmacodynamic Drug Interactions: Monitor for increased risk of bleeding; Use if benefits outweigh risks Applies to **all DOACs** if used along with antiplatelet therapies, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs).
Pharmacokinetic: Impact Elimination / Metabolism (see chart below) **Apixaban and rivaroxaban** are eliminated/metabolized by the P-glycoprotein efflux transporter system and the CYP3A4 hepatic isoenzyme system **Dabigatran and edoxaban** are eliminated by the P-glycoprotein efflux transporter system Inducers of these systems may REDUCE anticoagulant effects and INCREASE the risk of clotting. Inhibitors of these systems may INCREASE the risk of bleeding

	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Edoxaban (Savaysa)
AVOID Concomitant Use	**Inhibitors (increase bleed risk)** **Apixaban 2.5mg BID**: AVOID **[Apixaban higher doses**: ADJUST (see next section)] • Cobicistat • Ketoconazole (systemic) • Indinavir • Itraconazole (systemic) • Posaconazole • Ritonavir • Saquinavir	**Inhibitors (increase bleed risk)** **Patients with CrCl < 80 mL/min:** AVOID unless benefit justifies risk • Cyclosporine • Diltiazem • Dronedarone • Erythromycin (systemic) • Verapamil **Regardless of Renal Function:** AVOID • Cobicistat • Ketoconazole (systemic) • Indinavir • Itraconazole (systemic) • Posaconazole • Ritonavir • Saquinavir	**Inhibitors (increase bleed risk)** ***Atrial Fibrillation:*** **Patients with CrCl < 30 mL/min:** AVOID ***VTE:*** **Patients with CrCl < 50 mL/min:** AVOID • Azithromycin (systemic) • Carvedilol • Cobicistat • Cyclosporine (systemic) • Daclatasvir • Dronedarone • Elagolix • Eliglustat • Erythromycin (systemic) • Flibanserin • Fostamatinib • Glecaprevir/pibrentasvir • Itraconazole (systemic) • Ivacaftor • Ketoconazole (systemic) • Lapatinib • Ledipasvir • Neratinib • Osimertinib • Propafenone • Quinine • Ranolazine • Ritonavir • Rolapitant • Simeprevir • Tucatinib • Velpatasvir • Vemurafenib • Voclosporin	
	Inducers (increase clot risk) • Carbamazepine • Fosphenytoin • Phenytoin • Rifampin • St. John's Wort	**Inducers (increase clot risk)** • Carbamazepine • Fosphenytoin • Phenytoin • Rifampin • St. John's Wort	**Inducers (increase clot risk)** • Carbamazepine • Fosphenytoin • Phenytoin • Rifampin • St. John's Wort	**Inducers (increase clot risk)** • Carbamazepine • Fosphenytoin • Phenytoin • Rifampin • St. John's Wort

	Apixaban (Eliquis)	Rivaroxaban (Xarelto)	Dabigatran (Pradaxa)	Edoxaban (Savaysa)
ADJUST dose of DOAC ***If Concomitant Use*** 	**Inhibitors (increase bleed risk)** **Apixaban 5mg or 10 mg BID**: REDUCE Apixaban dose by 50% **Apixaban 2.5mg BID**: AVOID (see above section) • Cobicistat • Ketoconazole (systemic) • Indinavir • Itraconazole (systemic) • Posaconazole • Ritonavir • Saquinavir		**Inhibitors (increase bleed risk)** ***Atrial Fibrillation:*** **Patients with CrCl 30-50 mL/min**: CONSIDER REDUCING DOSE from 150 mg BID to 75 mg BID • Dronedarone • Ketoconazole (systemic)	**Inhibitors (increase bleed risk)** **VTE: Reduce edoxaban dose from 60 mg once daily to 30 mg once daily** • Azithromycin (systemic) • Clarithromycin • Dronedarone • Erythromycin • Itrconazole (systemic) • Ketoconazole (systemic) • Quinidine • Verapamil
MONITOR* ***If Concomitant Use*** Limited data, assess risk Dose adjustments not recommended 	**Inhibitors (increase bleed risk)** • Clarithromycin • Cyclosporine • Diltiazem • Dronaderone • Erythromycin (systemic) • Verapamil	**Inducers (increase clot risk)** • Enzalutamide • Lumacaftor • Mitotane • Phenobarbital • Primidone		

Table adapted from: ***https://acforum-excellence.org/Resource-Center/resource_files/-2020-10-08-202155.pdf***

**** Monitoring*** *includes regular assessment of bleeding or clotting, medication adherence and more frequent monitoring of hepatic and renal function - generally every six months or up to four times a year in older patients.*

Important Note

This chart does not represent an exhaustive list of medications that potentially interact with DOACs. Please consult a pharmacist or drug information reference for additional information on drug-drug interactions when needed.